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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/739,933
Filing Date: December 18, 2000
Appellant(s): REID ET AL.

Paula A. Borden
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4-22-05.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is incorrect. A correct statement of the status of the claims is as follows:

Claims 1-3, 5-8, 33 and 63-64 submitted 4-22-05 have been substituted for the rejected claims.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct. It is noted that the claims submitted 4-22-05 have been entered as indicated above. This submission was not after final rejection.

(5) Summary of Invention

The summary of invention contained in the brief is deficient because it does not refer to the other modes or routes of administration intended to be encompassed, in particular with respect to "parenteral administration" as claimed. In particular, the specification at pp. 33-37, refers to alternative routes of administration inclusive of in vitro, in vivo and via genetic manipulation, see especially p. 34, lines 9-17, "Those of ordinary skill in the art appreciate the need to formulate pharmaceutical compositions for their intended route of administration (which may include parenteral, e.g.,

intravenous, intradermal, or intramuscular injection; oral administration; or direct application to the affected area). It is contemplated that the present methods will be carried out by applying polypeptides to neural precursors harvested from the brain and placed in culture or directly to the precursor cells in vivo (by, e.g., infusion through an injection cannula or shunt, or by implantation within a carrier, e.g., a biodegradable capsule) but other routes of administration, particularly parenteral (preferably intravenous) administration, are also within the scope of the invention.", and especially p. 36, lines 10-20, "In lieu of direct application of polypeptides that bind the EGF receptor or stimulate cellular differentiation, nucleic acid molecules encoding those polypeptides can be inserted into vectors and used ms gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470) or by stereotactic injection see, e.g., Chen et al., Proc. Natl. Acad. Sci. USA c:3054-3057, 1994). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded, for example, in the brain or spinal cord. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, e.g., retroviral vectors, the pharmaceutical preparation can include one or more cells that produce the gene delivery system.".

(6) Issues

The appellant's statement of the issues in the brief is substantially correct. The changes are as follows: Issue I, with respect to 35 USC 112, second paragraph is moot in view of the claim amendments entered 4-22-05.

(7) Grouping of Claims

The rejection of claims 1-3, 5-8, 33 and 63-64 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7). Appellants referral to claims 64-65 is an apparent oversight.

(8) Claims Appealed

A substantially correct copy of appealed claims 1-3, 5-8, 33 and 63-64 appears on page 49 of the Appendix to the appellant's brief. The minor errors are as follows: The Appendix does not reflect the changes to the claims submitted 4-22-05 which have been entered.

(9) Prior Art of Record

5,980,885 Weiss Nov. 9, 1999

Fallon J. et al., "In vivo induction of massive proliferation, directed migration, and differentiation of neural cells in the adult mammalian brain" PNAS, vol 97, no. 26 (December 19, 2000), pp. 14686-14691.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102(e)

Claims 1-3, 5-8, 33, and 63-64 are rejected under 35 U.S.C. 102(e) as being anticipated by Weiss et al., 5,980,885, filed June 7, 1995 and issued Nov. 9, 1999.

Weiss et al., teach administration of TGF-α to patients in vivo for the purpose of inducing in vivo proliferation, migration and differentiation of neural and/or glial cell precursors and for treatment of injuries and diseases of the nervous system including Huntington's, Alzheimer's, Parkinson's and other neurological disorders, see in particular Abstract, lines 5-7, column 25, line 20-column 26, line 64 and Examples 27-30. In addition, the method may be used in areas of demyelination or autoimmune disease such as MS for proliferation of glial schwann, see in particular columns 24-25. The method is also disclosed for use in the replacement of neurons, for example as transplants or grafts, disclosed at column 23. Weiss further teaches that these effects may be achieved by direct administration, thus obviating particular problems associated with transplant, see in particular column 12-25 in regard to culture, modification and transplantation of cells and columns 25-29 for the alternative method of direct administration for production of the appropriate cells and treatment in vivo. The cells so produced may be generically used to replace damaged or missing neurons and/or glia, see in particular Abstract and column 25, lines 34-41. In particular Weiss teaches injection of growth factors to animals having CNS damages or lesion, see in particular column 22, lines 10-17. The method as amended is also directed to an individual having CNS damage or lesion. Weiss teaches administration to patients suffering from injury or damage to the CNS and for CNS diseases such as Huntington's, Alzheimer's, Parkinson's, etc., see in particular column 25, line 55-column 26, line 26. Thus, Weiss

clearly establishes that the treatment is to an individual having CNS damage or lesion as in claim 1.

Weiss is not limited to ventricular administration of growth factor. For example, Weiss teaches administration other than in the ventricle, see in particular oral administration, injection, injection cannula, timed release apparati at the desired site, see in particular column 25, line 20-column 26, line 15. New claim 1 as amended recites parenteral administration. Parenteral administration refers to administration outside of the digestive tract. Appellant's specification at p. 34, lines 9-17 states, "Those of ordinary skill in the art appreciate the need to formulate pharmaceutical compositions for their intended route of administration (which may include parenteral, e.g., intravenous, intradermal, or intramuscular injection; oral administration; or direct application to the affected area). It is contemplated that the present methods will be carried out by applying polypeptides to neural precursors harvested from the brain and placed in culture or directly to the precursor cells in vivo (by, e.g., infusion through an injection cannula or shunt, or by implantation within a carrier, c.g., a biodegradable capsule) but other routes of administration, particularly parenteral (preferably intravenous) administration, are also within the scope of the invention." Thus, Appellant's specification places oral administration, as in Weiss, within the "parenteral" route and thus Weiss anticipates. Weiss additionally teaches that administration may be through injection and thus includes administration other than by the digestive tract. Moreover, Weiss teaches multiple methods of growth factor administration including via mechanisms in addition to direct in vivo administration. For example column 10, lines

23-column 11, line 4, teach that the administration may be via culture of cells with TGF-alpha, via transplantation of cells maintained or produced under such culture conditions, or via genetic manipulation of cells to provide the growth factor to the host either in vitro or in vivo. The claims further specify that preferred areas suitable for transplantation of such cells either supported by TGF-alpha or which produce TGF-alpha are to areas of CNS brain tissue including the striatum, adjacent to the ventricle (the subependymal zone), and to spinal cord tissue, see in particular column 12, line 53-column 13, line 41. Weiss et al., teach that the administration of the TGF-alpha growth factor can be by any method, including injection cannula, transfection of cells with growth hormone-expressing vectors, transplantation of cells maintained in TGF-alpha, via direct injection, and via timed release apparati which can administer substances at the desired site, see in particular column 25, lines 40-column 26, line 15. Moreover, Weiss teaches that the direct administration may be so as to provide proliferation and differentiation of the cells as described by the noted genetic modifications, or culture and transplantation methods provided. Such mechanisms and sites of interest include transplantation or delivery to basal gangia, caudate, putamen, nucleus basalis or substantia nigra, i.e., into the striatum as claimed, see in particular column 23, lines 4-21, column 26, lines 21-26 and 61-64. Also the compositions may be administered via oral administrations, see in particular column 25, lines 40-55. (Claims 33 and 63 are not limited to parenteral administration). Additionally it is noted that a desired site is in the striatum as noted at column 26, lines 22-26 and 61-64. For treatment of spinal cord injury, MS or other deyelinating diseases growth factors would be delivered to spinal cord as in Examples

15-17. Further Example 44 teaches neural stem cell proliferation in spinal cord tissue from vertebral column, thoracic, and lumbar-sacral tissue and column 62 teaches mouse models of spinal cord injury and disease treatment via transplantation into lumbar lateral funiculus. Thus, Weiss acknowledges administration via various mechanisms, "outside the ventricles". This is also akin to that contemplated within Appellants specification, see especially p. 36, lines 10-20, "In lieu of direct application of polypeptides that bind the EGF receptor or stimulate cellular differentiation, nucleic acid molecules encoding those polypeptides can be inserted into vectors and used as gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470) or by stereotactic injection see, e.g., Chen et al., Proc. Natl. Acad. Sci. USA :3054-3057, 1994). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded, for example, in the brain or spinal cord. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, e.g., retroviral vectors, the pharmaceutical preparation can include one or more cells that produce the gene delivery system." Accordingly, the situations appear to squarely correspond.

Claim 63 recites intrastriatal administration and claim 64 via continuous infusion. Weiss teaches methods and compositions for the treatment of Parkinson's disease where new stem cells are generated in the striatum via administration of neural stem cell progeny resulting from genetically modified or cultured stem cells stimulated via

growth factors to the lateral ventricle or at the site of lesion, see in particular column 22, lines 10-18, column 26, lines 41-45 and column 60. Weiss also teaches where administration of the neural precursors/progeny may be administered at the lesion site, see in particular column 62, line 63-column 63, line 50 and hence injection. In addition, Weiss teaches infusion into the lateral ventricles for six consecutive days via continuous infusion, see in particular column 28, lines 1-9, 18-26, 60-67 and Example 27.

Further as to the mechanism of action of such administration, Weiss teaches that the neural stem cell progeny stimulated by TGF-alpha can migrate into regions that have been damaged as a result of injury or disease, see in particular column 26, lines 10-12. Weiss further teaches that in vivo infusion results in the induction of proliferation migration and differentiation of neural stem cells and progenitor cells in vivo, see in particular column 27, lines 20-24.

Even though the reference does not ipsis verbis teach administration "outside the ventricles" the reference teachings provide for administration of the growth factors outside the ventricles because the reference teaches the relevant sites outside the ventricles that are to be treated by the neural precursor cells that are stimulated to proliferate, differentiate and migrate via TGF-alpha exposure. The cells may be provided via the alternative conventions of in vitro proliferation with TGF-alpha followed by subsequent transplantation to the site, transplantation of cells genetically modified to provide TGF-alpha to the relevant site, and direct administration of the growth factor in vivo, see in particular Summary of the Invention, column 10, line 23-67 and column 11, lines 40-66. The relevant intrastriatal site is clearly identified as the desired site to

provide for replacement of dopaminergic neurons in Parkinson's disease. Thus the reference teaches that the direct in vivo administration may be via intrastriatal infusion and would provide for the necessary growth factor in the striatum or subependymal zone region "desired site" where proliferation to produce dopaminergic neurons is required. The reference teaches that that direct injection is appropriate to provide delivery at the desired site which is outside of the ventricle. Weiss teaches administration at the site of damage or lesion where promotion of growth, differentiation and migration of neural and glial cells would occur for the treatment of intrastriatal neurons in Parkinson's disease. Moreover, the reference teaches the desired site of spinal cord neurons and injection or administration to spinal cord neurons for treatment of spinal cord injury or multiple sclerosis. Further as noted above the administration via direct injection may be via injection cannula capable of providing continuous infusion. Thus, the reference teaches direct injection of the growth factor at the relevant site outside the ventricle and into the striatum or spinal cord. The reference teaches that direct administration is suitable and avoids the noted problems associated with transplantation of heterologous cells in vivo, see in particular column 12-15. The reference teaches that administration via continuous infusion over six days as directed by Weiss can provide for the proliferative and migratory effects of the precursors either in vitro over multiple days or in vivo via injection over multiple days. While Weiss specifically exemplifies continuous infusion into the ventricles the reference teachings are not so limited. Weiss teaches injection and injection cannula for delivery at cumulative sites and durations so as to provide proliferation, differentiation and

migration. Thus, the reference teachings anticipate the claimed invention. The art rejections have been alternatively set forth in a 103 rejection as the teachings are not ipsis verbis. However, the teachings apparently arise to that of anticipation as the reference is enabling to the artisan for practice of the claimed invention. The rejections above are not in conflict in that "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977).

While it is true that Weiss directs that a preferred embodiment of the invention is delivery of the growth factor to the ventricles, the Examiner notes that Weiss is not limited to a teaching of administration to the ventricles. Moreover, Weiss is directed to administration to patients with damage or lesion and for the purpose of attraction of neural progenitor cells to a site of damage or lesion in the CNS.

While the Weiss patent fails to ipsis verbis teach administration of TGF-alpha, "outside the ventricles," via, "intrastriatal administration," and wherein the site is, "spinal cord tissue and spinal nerve root origins," such limitations are anticipated by the reference as set forth above.

Claim Rejections - 35 USC § 103

Claims 1-3, 5-8, 33, and 63-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiss et al., 5,980,885, filed June 7, 1995 and issued Nov. 9, 1999.

The teachings of Weiss are as set forth above.

While the Weiss patent fails to ipsis verbis teach administration of TGF-alpha, "outside the ventricles," via, "intrastriatal administration," and wherein the site is, "spinal cord tissue and spinal nerve root origins," such limitations are rendered obvious by the reference as a whole.

Weiss et al., teach administration of TGF-α to patients in vivo for the purpose of inducing in vivo proliferation, migration and differentiation of neural and/or glial cell precursors and for treatment of injuries and diseases of the nervous system including Huntington's, Alzheimer's, Parkinson's and other neurological disorders, see in particular Abstract, lines 5-7, column 25, line 20-column 26, line 64 and Examples 27-30. In addition, the method may be used in areas of demyelination or autoimmune disease such as MS for proliferation of glial schwann, see in particular columns 24-25. The method is also disclosed for use in the replacement of neurons, for example as transplants or grafts, disclosed at column 23. Weiss further teaches that these effects may be achieved by direct administration, thus obviating particular problems associated with transplant, see in particular column 12-25 in regard to culture, modification and transplantation of cells and columns 25-29 for the alternative method of direct administration for production of the appropriate cells and treatment in vivo. The cells so produced may be generically used to replace damaged or missing neurons and/or glia, see in particular Abstract and column 25, lines 34-41. In particular Weiss teaches injection of growth factors to animals having CNS damages or lesion, see in particular column 22, lines 10-17. The method as amended is also directed to an individual having CNS damage or lesion. Weiss teaches administration to patients suffering from

injury or damage to the CNS and for CNS diseases such as Huntington's, Alzheimer's, Parkinson's, etc., see in particular column 25, line 55-column 26, line 26. Thus, Weiss clearly establishes that the treatment is to an individual having CNS damage or lesion as in claim 1.

Weiss is not limited to ventricular administration of growth factor. For example, Weiss teaches administration other than in the ventricle, see in particular oral administration, injection, injection cannula, timed release apparati at the desired site, see in particular column 25, line 20-column 26, line 15. New claim 1 as amended recites parenteral administration. Parenteral administration refers to administration outside of the digestive tract. Applicants specification at p. 34, lines 9-17 states, "Those of ordinary skill in the art appreciate the need to formulate pharmaceutical compositions for their intended route of administration (which may include parenteral, e.g., intravenous, intradermal, or intramuscular injection; oral administration; or direct application to the affected area). It is contemplated that the present methods will be carried out by applying polypeptides to neural precursors harvested from the brain and placed in culture or directly to the precursor cells in vivo (by, e.g., infusion through an injection cannula or shunt, or by implantation within a carrier, c.g., a biodegradable capsule) but other routes of administration, particularly parenteral (preferably intravenous) administration, are also within the scope of the invention." Thus, Appellants specification places squarely oral administration, as in Weiss, within the "parenteral" route and thus Weiss anticipates. Weiss additionally teaches that administration may be through injection and thus includes administration other than by the digestive tract.

Moreover, Weiss teaches multiple methods of growth factor administration including via mechanisms in addition to direct in vivo administration. For example column 10, lines 23-column 11, line 4, teach that the administration may be via culture of cells with TGF-alpha, via transplantation of cells maintained or produced under such culture conditions, or via genetic manipulation of cells to provide the growth factor to the host either in vitro or in vivo. The claims further specify that preferred areas suitable for transplantation of such cells either supported by TGF-alpha or which produce TGF-alpha are to areas of CNS brain tissue including the striatum, adjacent to the ventricle (the subependymal zone), and to spinal cord tissue, see in particular column 12, line 53-column 13, line 41. Weiss et al., teach that the administration of the TGF-alpha growth factor can be by any method, including injection cannula, transfection of cells with growth hormone-expressing vectors, transplantation of cells maintained in TGF-alpha, via direct injection, and via timed release apparati which can administer substances at the desired site, see in particular column 25, lines 40-column 26, line 15. Moreover, Weiss teaches that the direct administration may be so as to provide proliferation and differentiation of the cells as described by the noted genetic modifications, or culture and transplantation methods provided. Such mechanisms and sites of interest include transplantation or delivery to basal gangia, caudate, putamen, nucleus basalis or substantia nigra, i.e., into the striatum as claimed, see in particular column 23, lines 4-21, column 26, lines 21-26 and 61-64. Also the compositions may be administered via oral administrations, see in particular column 25, lines 40-55. (Claims 33 and 63 are not limited to parenteral administration). Additionally it is noted that a desired site is in the striatum as noted at

column 26, lines 22-26 and 61-64. For treatment of spinal cord injury, MS or other demyelinating diseases growth factors would be delivered to spinal cord as in Examples 15-17. Further Example 44 teaches neural stem cell proliferation in spinal cord tissue from vertebral column, thoracic, and lumbar-sacral tissue and column 62 teaches mouse models of spinal cord injury and disease treatment via transplantation into lumbar lateral funiculus. Thus, Weiss acknowledges administration via various mechanisms, "outside the ventricles". This is also akin to that contemplated within Appellants specification, see especially p. 36, lines 10-20, "In lieu of direct application of polypeptides that bind the EGF receptor or stimulate cellular differentiation, nucleic acid molecules encoding those polypeptides can be inserted into vectors and used ms gene therapy vectors. Gene therapy vectors can be delivered to a subject by, for example, intravenous injection, local administration (U.S. Patent 5,328,470) or by stereotactic injection see, e.g., Chen et al., Proc. Natl. Acad. Sci. USA :3054-3057, 1994). The pharmaceutical preparation of the gene therapy vector can include the gene therapy vector in an acceptable diluent, or can comprise a slow release matrix in which the gene delivery vehicle is imbedded, for example, in the brain or spinal cord. Alternatively, where the complete gene delivery vector can be produced intact from recombinant cells, c.g., retroviral vectors, the pharmaceutical preparation can include one or more cells that produce the gene delivery system." Accordingly, the situations squarely correspond.

Claim 63 recites intrastriatal administration and claim 64 via continuous infusion. Weiss teaches methods and compositions for the treatment of Parkinson's disease

where new stem cells are generated in the striatum via administration of neural stem cell progeny resulting from genetically modified or cultured stem cells stimulated via growth factors to the lateral ventricle or at the site of lesion, see in particular column 22, lines 10-18, column 26, lines 41-45 and column 60. Weiss also teaches where administration of the neural precursors/progeny may be administered at the lesion site, see in particular column 62, line 63-column 63, line 50 and hence injection. In addition, Weiss teaches infusion into the lateral ventricles for six consecutive days via continuous infusion, see in particular column 28, lines 1-9, 18-26, 60-67 and Example 27.

Further as to the mechanism of action of such administration, Weiss teaches that the neural stem cell progeny stimulated by TGF-alpha can migrate into regions that have been damaged as a result of injury or disease, see in particular column 26, lines 10-12. Weiss further teaches that in vivo infusion results in the induction of proliferation migration and differentiation of neural stem cells and progenitor cells in vivo, see in particular column 27, lines 20-24.

Weiss et al., fail to ipsis verbis teach administration "outside the ventricles", via "intrastriatal infusion" and to "spinal cord tissue and spinal nerve root origins".

However, Weiss renders obvious administration of the growth factors outside the ventricles because the reference teaches the relevant sites outside the ventricles that are to be treated by the neural precursor cells and that are stimulated to proliferate, differentiate and migrate via TGF-alpha exposure. The reference further teaches direct administration via oral administration, injection and injection cannula. The administration is in vivo. Alternatively the methods may be practiced indirectly via

transplantation of cells treated in culture or genetically modified cells which produce the growth factor. However, the artisan recognizes that direct administration at the site circumvents the need for transplantation procedures. Thus, direct administration provides the advantage of being simple and avoids histocompatibility rejection via the host. The cells may alternatively be provided via the conventions of in vitro proliferation with TGF-alpha followed by subsequent transplantation to the site, transplantation of cells genetically modified to provide TGF-alpha to the relevant site, and direct administration of the growth factor in vivo, see in particular Summary of the Invention, column 10, line 23-67 and column 11, lines 40-66. The relevant intrastriatal site is clearly identified as the desired site to provide for replacement of dopaminergic neurons in Parkinson's disease. Thus the reference renders obvious that the direct in vivo administration may be via intrastriatal infusion and would provide for the necessary growth factor in the striatum or subependymal zone region "desired site" where proliferation to produce dopaminergic neurons is required. The reference teaches that that direct injection is appropriate to provide delivery at the desired site which is outside of the ventricle. Weiss teaches administration at the site of damage or lesion where promotion of growth, differentiation and migration of neural and glial cells would occur for the treatment of intrastriatal neurons in Parkinson's disease. Moreover, the reference teaches the desired site of spinal cord neurons and injection or administration to spinal cord neurons for treatment of spinal cord injury or multiple sclerosis. Further as noted above the administration via direct injection may be via injection cannula capable of providing continuous infusion. Thus, the reference renders obvious direct

injection of the growth factor at the relevant site outside the ventricle and into the striatum or spinal cord. The reference teaches that direct administration is suitable and avoids the noted problems associated with transplantation of heterologous cells in vivo, see in particular column 12-15. The reference teaches that administration via continuous infusion over six days as directed by Weiss can provide for the proliferative and migratory effects of the precursors either in vitro over multiple days or in vivo via injection over multiple days. While Weiss specifically exemplifies continuous infusion into the ventricles the reference teachings are not so limited. Weiss teaches administration via injection and injection cannula for delivery at cumulative sites and durations so as to provide proliferation, differentiation and migration. Thus, the reference teachings render obvious the claimed invention directed to continuous infusion. The artisan would expect positive results using the various modifications given the success of Weiss in providing treatment of Parkinson's disease and spinal cord injury as exemplified in the '885 patent. Thus, the cumulative references teachings render the claimed invention obvious to one of skill in the art. The art rejections have been alternatively set forth in a 103 rejection as the teachings are not ipsis verbis. However, the teachings apparently arise to that of anticipation as set forth above. The reference is enabling to the artisan for the practice of the claimed invention. The rejections above are not in conflict in that "There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102." In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977).

While it is true that Weiss directs that a preferred embodiment of the invention is delivery of the growth factor to the ventricles, the Examiner notes that Weiss is not limited to a teaching of administration to the ventricles. Moreover, Weiss is directed to administration to patients with damage or lesion and for the purpose of attraction of neural progenitor cells to a site of damage or lesion in the CNS.

(11) Response to Argument

Appellant's arguments are as extensively set forth throughout pages 11-47, particularly pp. 14-47 of the Brief including reference to delimited excerpts from the specification and cited US Patent. As the arguments are extensive, the Examiner will not further duplicate them here but will respond to them in summary as presented.

Appellants extensively argue that Weiss is not effective to the specific teachings of administration of TGF-alpha or a functional fragment thereof, to an individual having CNS damage or lesion, to administration outside of the ventricles and to migration to the site of damage or lesion. Appellants further assert that their invention is the first to distinguish a particular "en masse" migration, see in particular Fallon et al., 2000, brought about by TGF-alpha administration to the brain, outside the ventricles, in the presence of lesion or damage. Appellants analyze select portions of the Weiss patent, particularly excerpts of Examples 27-30 and via their analysis conclude that the invention is not taught by Weiss. Appellants argue that Weiss's entire focus is to administration into the ventricles and that administration of TGF-alpha to the ventricles does not result in substantial migration of neural stem cells or their progeny thereof. Appellants argue that the particular embodiments of Weiss with respect to growth factor

administration via transplantation of cells genetically engineered to produce the factor do not meet the claim limitations of administration of a peptide. Appellants attempt to distinguish administration from "a site" and "a mode". Appellants argue that the Weiss results or increases are, "meager background levels", "therapeutically insignificant" and "nondirected". Appellants argue that the intraventricular administration does not result in the formation of the "striatal ridge" and effect migration.

Yet as extensively set forth in the rejection noted above, Weiss similarly teaches the stimulation of proliferation, migration and differentiation of neual progenitors in the presence of both TGF-alpha and in the presence of CNS damage or lesion that is effective to stimulate proliferation and migration of neural progenitor cells or progeny thereof to a site of damage or lesion in the CNS. The Examiner notes as set forth above that Weiss teaches the effectiveness of their procedure in providing for proliferation and migration of neuronal progenitor cells to sites of lesion. In particular, Weiss notes both of the required elements, i.e., damage or lesion and administration of TGF-alpha at or near sites of CNS damage or lesion including via administration to the patient outside the ventricle. The Patent is noted to be particularly effective for treatment and to provide for proliferation, differentiation and migration of precursors or progeny for neuronal regeneration. The Fallon reference is noted. However, the teachings of Weiss fairly meet the claim limitations and there is no distinction provided in Fallon that contradicts, subverts or teaches away from Weiss, in contrast the references similarly support each others findings with respect to the noted effects of TGF-alpha in promoting migration of neural stem cells or progeny thereof in vivo in the

presence of injury. Appellant's comments speak to the effectiveness of the Weiss procedure, even if only to show moderate increases in migrating progenitor cells. Nevertheless the Weiss reference is noted to be enabling for treatment, to be therapeutically significant and to provide for directed migration to lesioned or damaged sites, for example as when administered in the brain to particular sites such as in substantia nigra, (intrastriatal) as provided in Weiss, see for example columns 27-28, column 60-62. Thus, in contrast to Appellants reading, the reference provides for migration that is noted via Weiss to be therapeutically significant and directed. Thus, the Weiss teachings anticipate the claimed invention in that the reference provides for each and every element of the claims.

Weiss is not limited to administration of growth factors via transplantation of cells. Nevertheless Weiss does contemplate administration of the growth factors via such procedure. Administration via transplantation of cells for the production of growth factors such as TGF-alpha is just as effective to administer TGF-alpha as administration of the factor itself and as noted it meets the claim limitations of administration of the polypeptide because both procedures necessarily result in the delivery (administration) of the polypeptide growth factor. Although the transplantation procedure is achieved via a different process, via administration of cells that make the growth factor, it is well established in patent law that product by process limitations fail to distinguish over product disclosures. Regardless of the means of administration, either via direct injection or via transplantation of cells manipulated to provide for the growth factor, the step of "administering" the factor is achieved and the artisan well recognizes such

alternative methods of administration. As noted above both Weiss and Appellants own specification appear to consider this a suitable means of administering.

Appellants fail to recognize the full teachings of the invention in toto. While it is true that the reference teaches administration of growth factors via gene transfer techniques and transplantation of cells either expressing TGF-alpha or stimulated in vitro with TGF-alpha contact, the reference also teaches expansion in vivo involving non surgical approaches via pharmaceutical manipulation (col. 11 lines 40-67), administration of growth factors and specifically administration of TGF-alpha (col. 19, lines 11-43). Hence, while the reference does specify more complex methods of harvesting cells, achieving proliferation in vitro and transplanting cells back to the host, or administration via gene transfer protocols, the reference teachings are not so limited. For example, Appellants fail to recognize the broad teachings directed to stimulating proliferation and differentiation in vivo, thereby avoiding the need for transplantation, see also columns 9-10, 11 and 14-15. See also column 25 lines 21-26, "Neural stem cells and their progeny can be induced to proliferate and differentiate in vivo by administering to the host, any growth factor(s) or pharmaceutical composition that will induce proliferation and differentiation of the cells." Here the cells are in vivo and are induced via growth factor administration. The suitability of TGF-alpha is specifically noted, see also col. 25, line 54 as well as columns 25-28 in toto. Similarly, while the reference exemplifies administration to ventricles, administration may also be achieved via pharmaceutical administration of growth factors as noted in columns 25-26, at the desired sites (col. 25, line 45, col.) including into brain (col. 28, lines 23-26) and

providing growth factors to the area of transplantation via, "implantation into the brain in proximity to the graft of any device which can provide an infusion of the factor to the surrounding cells." Hence, the administration may be via infusion to areas such as striatum or otherwise via other than the ventricle. Migration is noted, col. 27, lines 20-24, "Thus infusion of EGF or similar growth factors induces the proliferation, migration and differentiation of neural stem cells and progenitor cells in vivo and can be used therapeutically to replace neural cells lost due to injury or disease." The sites are of noted damage or lesion. Both site "desired site", site of "injury or disease" and mode "injection", "infusion" are provided. Thus, the reference teachings anticipate the claimed invention.

Appellant's analysis fails to recognize the full teachings of the invention in toto. While it is true that the reference teaches administration of growth factors via gene transfer techniques and transplantation of cells either expressing TGF-alpha or stimulation in vitro with TGF-alpha contact, the reference also teaches expansion in vitro or in vivo involving non surgical approaches via pharmaceutical manipulation (col. 11 lines 40-67), notably therein, "Proliferation and differentiation in vivo can involve a non-surgical approach that coaxes neural stem cells to proliferate in vivo with pharmaceutical administration." Also, column 19, lines 11-66, particularly lines 11-12, "The present invention provides a method of influencing the relative proportion of these differentiated cell types by the addition of exogenous growth factors." The administration of growth factors, may be any of the related growth factors but preferably for proliferation-inducing growth factors is TGF-alpha, as specifically noted at column

16, lines 7-8, "Preferred proliferation-inducing growth factors include EGF and TGF-alpha." Also see column 19, lines 29-48, including TGF-alpha, see in particular column 19, line 39 including various administration procedures throughout specifically noting administration of TGF-alpha (col. 19, lines 11-43). Hence, while the reference does specify more complex methods of harvesting cells achieving proliferation in vitro and transplantation back to the host, or administration via gene transfer protocols, the reference teachings are not so limited. For example, there is no acknowledgement by Appellants of the broad teachings directed to stimulating proliferation and differentiation in vivo, thereby avoiding the need for transplantation, see also columns 9-10, 11, 14-15. See also column 25, especially lines 21-26, "Neural stem cells and their progeny can be induced to proliferate and differentiate in vivo by administering to the host, any growth factor or pharmaceutical composition that will induce proliferation and differentiation of the cells," already as noted above constituting TGF-alpha. Here the cells are in vivo and are induced via growth factor administration. The suitability of TGF-alpha is specifically noted, see also col. 25, line 54 as well as columns 25-28 in toto.

Similarly, while the reference exemplifies administration into ventricles, the reference clearly indicates that the administration is effective to achieve that claimed i.e., "parenterally administering", "administration" and "wherein the administration is outside of the ventricles," for example, administration may also be achieved via pharmaceutical administration of growth factors as noted in columns 25-26, "at the desired site" (col. 25, line 45). The growth factors can be administered suitable to bypass the blood brain barrier thereby entering the brain even when administered via

the ventricle, see in particular column 25, line 55-column 26, line 15. The factor may be administered by genetic manipulation of cells whereby the transplanted cells then make the growth factor, thereby achieving administration of the growth factor via production by the cells, see for example column 27, lines 34-59. Here the cells and therefore administration may be provided at nearly any site within the brain, see in particular column 20, line 65-column 21, line 9, column 21, lines 34-51, column 22, lines 10-19, and columns 23-24. Columns 25-28 are directed to in vivo proliferation, differentiation and genetic modification of neural stem cell progeny. Here, the administration may also include direct injection/infusion into the brain, see in particular column 25, lines 23-column 26, line 15, also column 28, lines 23-26, "Other methods for providing growth factors to the area of transplantation include the implantation into the brain in proximity to the graft of any device which can provide an infusion of the factor to the surrounding cells." Hence, the administration may be via "infusion" to areas such as striatum. The appropriate sites are duly noted, see for example column 26-27. Further, retroviral administration is evidenced to permeate the brain thereby achieving administration outside the ventricle, see in particular column 27 and Example 27. Migration is noted, col. 27, lines 20-24, "Thus infusion of EGF or similar growth factors induces the proliferation, migration and differentiation of neural stem cells and progenitor cells in vivo and can be used therapeutically to replace neural cells lost due to injury or disease." The sites are of noted damage or lesion. Both site "desired site", site of "injury or disease" and mode "injection", "infusion" are provided.

Accordingly, the reference fairly teaches and achieves administration of the growth

factor to multiple sites outside the ventricles, whereby the administering is parenteral, i.e., not via digestive delivery, although the reference suitably teaches oral administration amongst others, now irrelevant as amended.

Appellant's arguments appear to arise from a perceived "improvement" over the teachings of Weiss. In particular, Appellants point to the phenomena achieved in their reference of a "striatal ridge" that they maintain is not noted via Weiss. However, the formation of a striatal ridge is not the subject of instant claims. Moreover, there is no evidence that practice of the Weiss invention within the full scope of its teachings and embodiments would not result in the formation of such a ridge. The patent does not exemplify, nor is it required to exemplify every one of its teachings regarding administration. Appellants appear to conclude that because the exemplifications (working examples) shown within the Weiss patent are not noted to be effective to produce a striatal ridge (as in the Fallon reference), that the Weiss teachings cannot be considered either enabled or anticipatory. However, the Weiss teachings are not limited to the working examples disclosed in their specification. All of their teachings within the specification are relevant and the Weiss patent fairly teaches all that is required of the claims. The Weiss patent does disclose migration of neural progenitors from the subependymal area to the striatum, see in particular column 27, lines 18-26, "Interestingly, this expansion of the number of B-gal labeled cells is accompanied by the migration of these cells away from the subepedymal medially, laterally, rostrally, and caudally with subsequent differentiation." While, Weiss does not term such migration as a "striatal ridge" the description is particularly similar, if not apparently the same and

particular to an "en masse" migration. This migration is achieved utilizing the procedures noted in Example 27 whereby retrovirus and EGF are infused intraventricularly. The example subsequently evidencing that the intraventricular administration achieves, as marked via B-gal expression, retrovirus delivery that is effectively disseminated into the brain, thereby marking whereby administration into the ventricles achieves pharmaceutical delivery or administration outside the ventricles into the brain. Appellants appear to conclude for example that the only teachings of administration by Weiss are intraventricular merely because intraventricular administrations are the subject of particular preferred embodiments and working examples. However, as noted above, the reference teaches numerous means of administration including, via injection cannula, transfection of cells with growth hormone-expressing vectors, injection, and timed release apparati which can administer substances at the desired site, see in particular column 25, lines 40-column 26, line 15 and also administration at the site of damage or lesion where promotion of growth, differentiation and migration of neural and glial cells would occur. Moreover, even the ventricular administration, not preferred by Appellants, is taught by Weiss as being effective to provide and achieve administration to sites outside the ventricle, thereby achieving administration outside the ventricles as claimed, presumably by pharmaceutical diffusion, in particular to brain regions adjacent or near the ventricle. Specifically, Weiss teaches that "Furthermore, the close proximity of the ventricles to many brain regions would allow for the diffusion of a secreted neurological agent by the stem cells or their progeny," column 26, lines 12-15 as well as paragraph spanning

columns 25-26 in toto. At column 60 Weiss teaches Huntington's and Parkinson's Disease models wherein transplants prepared as in examples 1-5 and 9 are injected into the striatum or substantia nigra at the site of lesion as described. As previously noted the transplants may be engineered to make TGF-alpha thereby administering it in vivo upon transplantation, and may also be accompanied, preceded or followed by additional TGF-alpha growth factor administration directly. Either way the TGF-alpha is evidenced to be administered either via injection at sites other than ventricle, may be achieved by infusion, diffusion therefrom, via modulation to pass the blood brain barrier or any other contemplated method as disclosed via Weiss which are deemed to be effective to provide administration/administering outside the ventricles. The patent reference does not teach away. All of its teachings must be considered, and it cannot be disparaged merely because it discloses additional means and/or embodiments including intraventricular administration, amongst others, not preferred by Appellants. Most notably, the reference teachings cannot be distinguished from the claims and thus, the reference teachings anticipate the claimed invention.

With respect to the aforementioned rejection under 35 USC 103, Appellants additionally argue that that the Examiner has not established a prima facie case. Appellants argue that there is no suggestion or motivation in Weiss or in the knowledge of the artisan to suitably modify Weiss to provide administration via other than by direct administration to the ventricle. Appellants argue no expectation of success for the claimed invention and argue that Weiss does not teach or suggest all claim limitations with respect to both the presence of a CNS damage or lesion and administration of a

TGF-alpha polypeptide or a functional fragment thereof that results in migration of progenitor cells or progeny away from the ventricles towards the site of CNS damage or lesion. Appellants argue that the rejection is one of hindsight reconstruction, that the art was not considered as a whole and the only teachings of Weiss are to ventricular administration and not on point to migration.

In contrast to the Appellants position, it is the Appellants reading that does not consider the full teachings of Weiss in toto. As extensively set forth, Weiss contemplates more than administration via intraventricular injection. It teaches effective treatment for neurological disorders and evidences migration away from the ventricles as extensively set forth above. In response to appellant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Accordingly, the Weiss teachings which are on point to all claim limitations provides both a motivation to combine or suitably modify as well as an expectation of success sufficient to render the claimed invention obvious.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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